



EAMS 11972/0002 Remdesivir 100 mg concentrate for solution for infusion

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here:

<http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm>

This information is intended for physicians and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the physician in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:

https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product. Whilst the scientific opinion is for use of the product to treat COVID-19, the opinion has been issued under EAMS and is not an exceptional authorisation or recommendation in response to the pandemic. [

The physician should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for the healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Remdesivir 100 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of remdesivir.

Each mL of concentrate contains 5 mg of remdesivir.

Each vial contains 6.0g of Betadex sulfobutyl ether sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colorless to yellow, aqueous-based concentrated solution.

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

Remdesivir is indicated for the treatment of adults and adolescent patients aged ≥ 12 years and weighing at least 40 kg hospitalised with suspected or laboratory confirmed SARS-CoV-2 infection and severe disease.

Patients with severe disease are those with an $SpO_2 \leq 94\%$ on room air or requiring supplemental oxygen, or requiring non-invasive or invasive ventilation or extracorporeal membrane oxygenation (ECMO).

4.2 Posology and method of administration

Remdesivir treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of COVID-19.

Posology

Adult patients and adolescent patients aged ≥ 12 years and weighing at least 40 kg

- The suggested dosage in adults and adolescents requiring invasive ventilation and/or ECMO is a single loading dose of remdesivir 200 mg on Day 1 followed by once-daily maintenance doses of remdesivir 100 mg for 9 days.
- The suggested dosage in adults and adolescents not requiring invasive ventilation and/or ECMO is a single dose of remdesivir 200 mg on Day 1 followed by once-daily maintenance doses of remdesivir 100 mg for 4 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e. up to a total of 10 days).
- Remdesivir is to be administered via intravenous infusion in a total volume of up to 250 mL 0.9% saline over 30 to 120 minutes.

Patients must have an estimated glomerular filtration rate (eGFR) determined before initial dosing and daily while receiving remdesivir (See section 4.4 & 5.2).

Hepatic laboratory testing should be performed in all patients before initial dosing and daily while receiving remdesivir (See sections 4.4 & 5.2).

Special populations

Paediatric Patients

There are insufficient data on dosing in paediatric patients under 12 years of age. Remdesivir may be used in adolescent patients 12 years of age and older at the same posology as in adults.

Elderly

No dose adjustment of remdesivir is proposed in patients over the age of 65 years (see sections 5.1 and 5.2).

Renal impairment

The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Patients must have an eGFR determined before dosing and daily while receiving remdesivir.

Remdesivir is not recommended in adult and adolescent patients with eGFR less than 30 mL/min or on renal replacement therapy. Caution is needed in patients with eGFR less than 50 mL/min (see section 4.4 and 5.2).

Hepatic impairment

The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is needed in patients with hepatic impairment.

Remdesivir should not be initiated in patients with ALT \geq 5 times the upper limit of normal at baseline. Remdesivir should be discontinued in patients who develop ALT \geq 5 times the upper limit of normal during treatment with remdesivir or ALT elevation accompanied by signs of symptoms of liver inflammation or increasing conjugated bilirubin or alkaline phosphatase.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir (see section 4.4 and 5.2).

Pregnancy

No adequate and well-controlled studies of remdesivir use in pregnant women have been conducted. Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus.

Breast-feeding

There is no information regarding the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, remdesivir and metabolites have been detected in the nursing pups of mothers given remdesivir, likely due to the presence of remdesivir in milk. Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the drug in breastfeeding infants, breastfeeding is not recommended.

Method of administration

Remdesivir is administered intravenously by infusion.

Remdesivir should be infused over 30 to 120 minutes as described in Table 1. After infusion is complete, flush with at least 30 mL of 0.9% saline. Discard any unused remdesivir concentrate for solution for infusion and diluted solution for infusion. Do not administer as an intramuscular (IM) injection.

Table 1: Recommended rate of infusion— for diluted remdesivir concentrate for solution for infusion in adults and adolescent patients (12 years of age and older) \geq 40 kg

Infusion bag volume	Infusion time	Rate of infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There are limited clinical data available for remdesivir. Serious and unexpected adverse events may occur that have not been previously reported with remdesivir use.

Transaminase elevations

Transaminase elevations, have been observed in the remdesivir clinical development program, including in healthy volunteers and patients with COVID-19. Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

- Remdesivir should not be initiated in patients with ALT \geq 5 times the upper limit of normal at baseline.
- Remdesivir should be discontinued in patients who develop:
 - ALT \geq 5 times the upper limit of normal during treatment with remdesivir.
 - OR
 - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin or alkaline phosphatase (see section 4.2 and 5.2).

Renal Impairment

All patients must have creatinine clearance determined before dosing.

The excipient betadex sulfobutyl ether sodium (SBECD) is renally cleared and accumulates in patients with decreased renal function, therefore administration of drugs formulated with SBECD (such as remdesivir) is not recommended in patients with eGFR less than 30 mL/min unless the potential benefit outweighs the potential risk (see section 4.2 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with remdesivir.

Drug-drug interaction trials of remdesivir and other concomitant medications have not been conducted in humans. *In vitro*, remdesivir is a substrate for drug metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. *In vitro*, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP. The clinical relevance of these *in vitro* drug assessments has not been established.

4.6 Fertility, pregnancy and lactation

Pregnancy

No adequate and well-controlled studies of remdesivir use in pregnant women have been conducted. Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus.

In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryofoetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD) (see section 5.3).

Breast-feeding

There is no information regarding the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, remdesivir and metabolites have been detected in the nursing pups of mothers given remdesivir, likely due to the presence of remdesivir in milk. Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the drug in breastfeeding infants breastfeeding is not recommended (see section 5.3).

Fertility

No human data on the effect of remdesivir on fertility are available. Nonclinical toxicity studies demonstrated no adverse effect on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of remdesivir on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

In healthy subjects and hospitalized patients with PCR-confirmed SARS-CoV-2 infection, graded elevations in ALT and AST have been observed with a loading dose of remdesivir 200 mg administered intravenously on Day 1 followed by 100 mg administered intravenously once daily for up to 9 days. The mechanism of these elevations is unknown.

Patients should have appropriate clinical and laboratory monitoring to aid in early detection of any potential adverse events. The decision to continue or discontinue remdesivir after development of an adverse event should be made based on the clinical risk benefit assessment for the individual.

Clinical Trials Experience

In a randomized, open-label clinical trial (Study GS-US-540-5773) of remdesivir in 397 subjects with severe COVID-19 treated with remdesivir for 5 (n=200) or 10 days (n=197), adverse events were reported in 71% and 74% of subjects, respectively, serious adverse events were reported in 21% and 35% of subjects, respectively, and Grade ≥ 3 adverse events were reported in 31% and 43% of subjects, respectively. Nine (5%) subjects in the 5-day group and 20 (10%) subjects in the 10-day group discontinued treatment due to an adverse event. All-cause mortality at Day 28 was 10% vs 13% in the 5- and 10-day treatment groups, respectively.

Description of selected adverse reactions

Hepatic adverse reactions

Clinical Trials Experience:

Experience in Healthy Volunteers

Grade 1 and 2 transaminase elevations were observed in healthy volunteers in Study GS-US-399-5505 (200 mg followed by 100 mg dosing for 5–10 days) and Study GS-US-399-1954 (150 mg daily for 7 or 14 days), which resolved after discontinuation of remdesivir.

Compassionate Use Experience:

Experience in Patients with COVID-19

In the compassionate use program in patients with severe or critical illness with COVID-19, liver function test abnormalities were reported in 11.7% (19/163) of patients. Time to onset from first dose ranged from 1-16 days. Four of these patients discontinued remdesivir treatment with elevated transaminases occurring on Day 5 of remdesivir treatment as per protocol.

Seven cases of serious liver-related laboratory abnormality were identified. There was 1 serious adverse event (SAE) of blood bilirubin increased in a critically ill patient with septic shock and multiorgan failure. None of the other cases had reported adverse events suggestive of hyperbilirubinemia or symptoms of hepatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the dedicated COVID-19 Yellow Card reporting site at coronavirus-yellowcard.mhra.gov.uk

4.9 Overdose

There is no human experience of acute overdosage with remdesivir. Treatment of overdose with remdesivir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with remdesivir.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to form the pharmacologically active nucleoside triphosphate metabolite. Metabolism of remdesivir to remdesivir triphosphate has been demonstrated in multiple cell types. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA. Remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases with low potential for mitochondrial toxicity.

Antiviral Activity

Remdesivir exhibited cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells with a 50% effective concentration (EC₅₀) of 9.9 nM after 48 hours of treatment. The EC₅₀ values of remdesivir against SARS-CoV-2 in Vero cells was 137 nM at 24 hours and 750 nM at 48 hours post-treatment.

Resistance

No clinical data are available on the development of SARS-CoV-2 resistance to remdesivir. The cell culture development of SARS-CoV-2 resistance to remdesivir has not been assessed to date.

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified 2 substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase at residues conserved across CoVs that conferred a 5.6 fold reduced susceptibility to remdesivir. The mutant viruses showed reduced viral fitness in cell culture and introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6-fold reduced susceptibility to remdesivir cell culture and attenuated SARS-CoV pathogenesis in a mouse model.

Clinical efficacy and safety

Clinical Trials in Subjects with COVID-19:

NIAID ACTT-1 Study

A randomized, double-blind, placebo-controlled clinical trial evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalized adult patients with COVID-19. The trial enrolled 1063 hospitalized patients in a 1:1 manner to receive remdesivir or placebo. The primary clinical endpoint was time to recovery within 28 days after randomization. In a preliminary analysis of the primary endpoint performed after 606 recoveries were attained, the median time to recovery was 11 days in the remdesivir group compared to 15 days in the placebo group (hazard ratio 1.31; 95% CI 1.12 to 1.54, p<0.001). Mortality was 8.0% for the remdesivir group versus 11.6% for the placebo group (p=0.059).

Study GS-US-540-5773

A randomized, open-label multi-center clinical trial (Study GS-US-540-5773) of patients with severe COVID-19 compared 197 adult patients who received remdesivir 200 mg once daily followed by remdesivir 100 mg once daily for 9 days (for a total of 10 days of intravenously administered therapy) with 200 adult patients who received remdesivir 200 mg once daily followed by remdesivir 100 mg for 4 days (for a total of 5 days of intravenously administered therapy), plus standard of care. The primary clinical endpoint was clinical status assessed by a 7-point ordinal scale at Day 14 after randomization. The study suggested that patients receiving a 10-day treatment course of remdesivir had similar improvement in clinical status

compared with those receiving a 5-day treatment course (10-to-5 day odds ratio: 0.76; 95% CI 0.51 to 1.13] on Day 14).

Clinical improvement was defined as an improvement of two or more points from baseline on a predefined 7-point scale, ranging from hospital discharge to increasing levels of oxygen support to death. Patients achieved clinical recovery if they no longer required oxygen support or were discharged from the hospital.

The time to clinical improvement for 50% of patients was 10 days in the 5-day treatment group and 11 days in the 10-day treatment group. At Day 14, observed rates between the 5- and 10- day treatment groups were 65% vs 54% for clinical improvement (70% vs 59% for clinical recovery and 8% vs 11% for mortality).

Compassionate Use Program in Patients with COVID-19

Remdesivir was evaluated in a compassionate use multi-center, open-label program in 163 adults with COVID-19 (N=79 outside of Italy). These patients were hospitalized with confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR) and manifestations of severe disease. Patients were treated with an initial intravenous loading dose of remdesivir 200 mg once daily for one day followed by a maintenance intravenous dose of remdesivir 100 mg once daily for up to 9 days, plus standard of care, for a total of up to 10 days of therapy. The mean treatment duration was 9 days; median follow-up time from first dose of remdesivir was 15 days (range 4-44 days).

The efficacy endpoint was clinical improvement, defined as improvement in oxygen support class during follow-up on a 7-category ordinal scale.

Overall, 48% of patients showed clinical improvement over median 15 days follow-up; 30% were discharged. Clinical improvement was demonstrated in 37% of patients on baseline invasive oxygen support, and in 67% of patients not on baseline invasive oxygen support. Overall mortality was 20% (N=33).

Reduction by 2 points in the 7-category ordinal scale was observed in 41% of patients overall, 29% of patients on baseline invasive oxygen support, and 62% of patients not on baseline invasive oxygen support.

Clinical Studies in Healthy Adults

Remdesivir was evaluated in four Phase 1 studies in 138 healthy adult volunteers (Studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US-399-5505). In these studies, transient graded elevations in ALT and AST were observed at repeated once-daily doses of remdesivir.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of remdesivir have been evaluated in adults in several Phase 1 trials.

- Following single-dose, 2-hour IV administration of remdesivir solution formulation at doses ranging from 3 to 225 mg, remdesivir exhibited a linear PK profile.
- Following single-dose, 2-hour IV administration of remdesivir at doses of 75 and 150 mg, both the powder for concentrate for solution for infusion and concentrate for solution for infusion formulations provided comparable PK parameters (AUC_{inf} , AUC_{last} , and C_{max}), indicating similar formulation performance.
- Remdesivir 75 mg powder for concentrate for solution for infusion formulation administered IV over 30 minutes provided similar peripheral blood mononuclear cell (PBMC) exposure of the active triphosphate metabolite GS-443902 as remdesivir 150 mg powder for concentrate for solution for infusion formulation administered IV over 2 hours.
- Following a single 150 mg intravenous dose of [^{14}C]-remdesivir, mean total recovery of the dose was greater than 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. The majority of remdesivir dose recovered in urine was metabolite GS-441524 (49%), while 10% was recovered as remdesivir.

Other special populations

Gender, Race and Age

Pharmacokinetic differences for gender, race, and age have not been evaluated.

Paediatric Patients

The pharmacokinetics of remdesivir in paediatric patients has not been evaluated.

Renal Impairment

Because the excipient SBECD is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with SBECD (such as remdesivir) is not recommended in patients with eGFR less than 30 mL/min unless the potential benefit outweighs the potential risk.

Hepatic Impairment

The pharmacokinetics of remdesivir and GS-441524 in hepatic impairment has not been evaluated.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.

Carcinogenesis

Given the short-term administration of remdesivir for the treatment of COVID-19, long-term animal studies to evaluate the carcinogenic potential of remdesivir are not required.

Mutagenesis

Remdesivir was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and *in vivo* rat micronucleus assays.

Animal Pregnancy Data

Remdesivir was administered via intravenous injection to pregnant rats and rabbits (up to 20 mg/kg/day) on Gestation Days 6 through 17, and 7 through 20, respectively, and also to rats from Gestation Day 6 to Lactation/Post-partum Day 20. No adverse effects on embryo-foetal (rats and rabbits) or pre/postnatal (rats) development were observed in rats and rabbits at nontoxic doses in pregnant animals. During organogenesis, exposures to the predominant circulating metabolite (GS-441524) were 4 (rats and rabbits) times higher than the exposure in humans at the RHD. In a pre/postnatal development study, exposures to the predominant circulating metabolite of remdesivir (GS-441524) were similar to the human exposures at the RHD.

Animal Breast-feeding Data

Remdesivir and its metabolites were detected in the plasma of nursing rat pups, likely due to the presence of remdesivir and/or its metabolites in milk, following daily intravenous administration of remdesivir to pregnant mothers from Gestation Day 6 to Lactation Day 20. Exposures in nursing pups were approximately 1% that of maternal exposure on lactation day 10.

Impairment of Fertility

Nonclinical toxicity studies in rats demonstrated no adverse effect on male fertility at exposures of the predominant circulating metabolite (GS-441524) approximately 2 times the exposure in humans at the RHD.

Reproductive toxicity, including decreases in corpora lutea, numbers of implantation sites, and viable embryos, was seen when remdesivir was administered intravenous daily at a systemically toxic dose (10 mg/kg) in female rats 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD.

Animal Toxicology and/or Pharmacology

Intravenous administration (slow bolus) of remdesivir to male rhesus monkeys at dosage levels of 5, 10, and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts.

Intravenous administration (slow bolus) of remdesivir to rats at dosage levels of ≥ 3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction.

Animal Pharmacology and efficacy data

It is unknown, at present, how the observed antiviral activity of remdesivir in animal models of SARS-CoV-2 infection will translate into clinical efficacy in patients with symptomatic disease. Key attributes of the

remdesivir nonclinical profile supporting its development for the treatment of COVID-19 are provided below:

- Remdesivir showed cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary HAE cells (EC₅₀ = 9.9 nM). The EC₅₀ values of remdesivir against SARS-CoV-2 in Vero cells has been reported to be 137 nM at 24 hours and 750 nM at 48 hours post-treatment.
- Remdesivir showed antiviral activity in SARS-CoV-2-infected rhesus monkeys. Administration of remdesivir at 10/5 mg/kg (10 mg/kg first dose, followed by 5 mg/kg once daily thereafter) using IV bolus injection initiated 12 hours post-inoculation with SARS-CoV-2 resulted in a reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and lung viral RNA levels compared with vehicle-treated animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex Sulfobutyl Ether Sodium
Hydrochloric acid or sodium hydroxide (to adjust pH)
Water for Injection

6.2 Incompatibilities

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of remdesivir solution for infusion with IV solutions and medications other than 0.9% saline is not known.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials
12 months

Concentrate for solution for infusion

Store at 2 °C to 8 °C until required for use. Dilute within the same day as administration.

Prior to dilution, equilibrate remdesivir concentrate for solution for infusion to room temperature (20°C to 25°C). Sealed vials can be stored up to 12 hours at room temperature prior to dilution.

Diluted solution for infusion

Store diluted remdesivir solution for infusion up to 4 hours at room temperature (20°C to 25°C) or 24 hours at refrigerated temperature (2°C to 8°C).

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).

For storage conditions after dilution of the medicinal product, see 6.3.

6.5 Nature and contents of container

Type I clear glass vial, an elastomeric closure, and an aluminium overseal with a flip-off cap.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Preparation of remdesivir solution for infusion - Adults and adolescent patients (12 years of age and older) ≥ 40 kg:

Dilution

Care should be taken to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible.

Remove the required number of single-use vial(s) from storage. For each vial:

- Equilibrate to room temperature (20°C to 25°C). Sealed vials can be stored up to 12 hours at room temperature prior to dilution.
- Inspect the vial to ensure the container closure is free from defects and the concentrate for solution for infusion is free of particulate matter.
- Using Table 2, determine the volume of 0.9% saline to withdraw from the infusion bag.

Table 2: Recommended remdesivir concentrate for solution dilution instructions – in adults and adolescent patients (12 years of age and older) ≥ 40 kg

Remdesivir dose	0.9% saline infusion bag volume to be used	Volume of saline to be withdrawn and discarded from 0.9% saline infusion bag	Required volume of reconstituted remdesivir concentrate for solution for infusion
200 mg (2 vials)	250 mL	40 mL	2 × 20 mL
100 mg (1 vial)		20 mL	20 mL

- Withdraw the required volume of saline from the bag using an appropriately sized syringe and needle. Discard the saline that was withdrawn from the bag.
- Withdraw the required volume of remdesivir concentrate for solution for infusion from the remdesivir vial using an appropriately sized syringe per Table 2.
 - Pull the syringe plunger rod back to fill the syringe with approximately 10 mL of air.
 - Inject the air into the remdesivir concentrate for solution for infusion vial above the level of the solution.
 - Invert the vial and withdraw the required volume of remdesivir concentrate for solution for infusion into the syringe. The last 5 mL of solution requires more force to withdraw.
- Discard any unused solution remaining in the remdesivir vial.
- Transfer the required volume of remdesivir concentrate for solution for infusion to the infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.

For storage conditions after dilution of the medicinal product, see 6.3.

Disposal

This product contains no preservative. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Gilead Sciences Limited
280 High Holborn
London
WC1V 7EE

8. EAMS NUMBER

11972/0002

9. DATE OF SCIENTIFIC OPINION

26th May 2020

Additional information

Each prescribing physician will be provided with a physician's pack containing all the relevant documents needed to manage patients receiving remdesivir under EAMS.

Details for reporting safety data:

- Email: Safety_FC@gilead.com
- Tel: +44 1223 897 500
- Fax: +1 650 522 5477

Questions once enrolling/enrolled:

- UKICOVID-19@gilead.com

General Medical Information enquiries:

- Email: UKMed.Info@gilead.com Tel: 08000 113 700.